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Case report

Lack of efficacy during the switch from brand to generic allopurinol

Antonio De Vuono MD Medical Practitioner [a],
Francesca Scicchitano PhD Clinical Pharmacist [b],
Caterina Palleria MD Clinical Pharmacology [b],
Emilio Russo PhD Assistant Professor [b,c],
Giovambattista De Sarro MD Full Professor [b,c],
Luca Gallelli MD, PhD Assistant Professor [b,c,*]

[a] ASP Cosenza, Italy
[b] Centro Regionale di Informazione sul farmaco, AO Mater Domini, Catanzaro, Italy
[c] Dipartimento di Medicina della Salute, Scuola di Medicina, Università di Catanzaro, Italy

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ABSTRACT

We report for the first time the lack of therapeutic effects after the switch from a brand formulation of allopurinol to a generic one. A 56-year-old man, with a 5 years history of well-treated gout arthropathy with allopurinol (Zyloric® 300 mg/die), developed acute gout arthropathy after the switch from the brand formulation of allopurinol to a generic one. Clinical evaluation and laboratory findings confirmed the diagnosis of acute gout arthropathy. Generic formulation of the drug was dismissed and Zyloric® was administered with an improvement of both clinical symptoms and laboratory findings. In conclusion, even if generic formulations are considered to have the same effects in comparison to the brand one, more data are necessaries in order to well define their effectiveness and rationale use.

1. Introduction

Allopurinol has been used in the United States since August 19, 1966, when it was first approved by Food and Drug Administration (FDA) under the trade name of Zyloprim, with the aim of reducing uric acid in the body through the inhibition of the enzyme xanthine oxidase that catalyses the transformation of hypoxanthine and xanthine to uric acid. Therefore, it is the first-line drug for serum urate-lowering therapy in gout and it is generally well tolerated, with a very low rate of clinically important adverse events. Recently, several generic drugs have been introduced in Italy in agreement with the Finance Law of 1996 (Law n. 549/1995 in G.U. n. 302 of 29.12.1995). Generic drugs are equivalent to brand one if they have the same active substance (with a difference of ±5%), the same pharmaceutical form, the same therapeutic indications, and a similar bioequivalence (±20%) to the reference medicinal product (Law n. 425/1996 in G.U. n. 208 of 05.09.1996. Legislative Decree no. 219/06).[1] At the time of the present paper, there are limited data concerning the real therapeutic bioequivalence between brand and generic formulation.[2] Moreover, other authors documented significant differences in peak concentrations between these formulations.[3,4] Since the number of spontaneous reporting of adverse drug reactions (ADRs) is usually underestimated,[5] we documented the development of side effects in well treated patients,[6–17] therefore it is possible that differences in active substances as well as in bioequivalence can induce the development of side effects or the lack of therapeutic effects. In the USA, the orange book publishes the list of drugs approved by FDA with therapeutic equivalence evaluations (defined as AA or AB). Unfortunately, in Italy there is not a similar book and the Italian Medicines Agency (AIFA), which is the national authority responsible for drugs regulation in Italy, does not define any parameter related to a real therapeutic equivalence. In this light, it is possible that a switch from brand formulation to generic one may induce a failure of clinical efficacy or the development of adverse drug reactions (ADRs). In this paper, we describe for the first time the lack of therapeutic effects after the switch from a brand allopurinol formulation to a generic one.

* Corresponding author. Department of Health Science, School of Medicine, University of Catanzaro, Viale Europa, 88100 Catanzaro, Italy. Tel.: +39 0961 712322; fax: +39 0961 774424.
E-mail address: gallelli@unicz.it (L. Gallelli).

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Table 1
Differences in excipients between brand (Zyloric®) and generic (Molteni®) formulation of allopurinol.

Zyloric (300 mg)	Molteni (300 mg)
Povidone	Povidone
Corn starch	Carboxymethylamide
Lactose	Microcrystalline cellulose
Magnesium stearate granulated lactose	Magnesium stearate
Dextrose	

2. Case report

A 56-year-old man, without history of smoke or alcohol consumption, and with a 5 years history of gout arthropathy well controlled by allopurinol (Zyloric® 300 mg/die), presented to his medical practitioner (MP) for the development of acute gout arthropathy.

Clinical evaluation revealed the presence of pain, heat, and redness of the joint tissues of the hands. Laboratory findings revealed increased serum levels of uric acid (11 mg/dL; normal range: 3.2–8.1), velocity of erythrocyte sedimentation (22 mm/h; normal range <20 mm/h) and C-reactive protein (9.5 mg/dL; normal range <0.50 mg/dl) and a diagnosis of acute gout arthropathy was found. Two days later, the persistence of symptoms induced a new clinical evaluation and, after a detailed history, MP documented that the patient, 2 weeks before the beginning of the symptoms, took the generic allopurinol (Molteni®) instead of the brand formulation (Zyloric®). Generic formulation was dismissed and Zyloric® was started with an improvement of clinical symptoms in about 3 days and of laboratory values in about 8 days (uric acid 5.6 mg/dL, VES 18 mm/h, C-reactive protein 4.9 mg/dL).

3. Discussion

In this paper, we report a patient that developed an acute attack of gout after the switch from a brand allopurinol formulation to a generic one.

Several factors may be involved in the genesis of acute gout in patients with chronic gout; however, in our patient both clinical manifestation and history revealed that the acute attack of gout was not related with systemic diseases or food consumption.

Previously, we described that dispensing errors may play a role in the development of ADRs or in the lack of efficacy.[18,19]

In our patient, we can exclude an error in the timing of drug administration or in the drug used, as referred by the patient and his parents.

Allopurinol has an half-life of 1 h and is quickly transformed in oxypurinol (half-life 15–30 h) and both are excreted through glomerular filtration. Since several drug–drug interactions may develop during a therapeutic treatment,[20–23] we can exclude that the lack of efficacy could be related to a drug–drug interaction since our patient did not use any other drug during the time of this study.

Recently, other authors reported a lack of efficacy after the switch from brand formulation to generic one,[24,25] therefore, we can suppose that in our patient the lack of efficacy might be related to the use of generic formulation.

We can hypothesize that two mechanisms might have been involved:

3.1. Difference of ±5% of active substance or ±20% of bioequivalence between brand formulation and generic one

This difference could play a role in the effectiveness of the drug, particularly in patients with a rapid cytochrome P450 (CYP450) metabolism, as previously documented.[16,26] In the present study, even if we did not evaluate the genetic pathway of CYP450, it may be possible that the presence of a rapid metabolism is involved in the lack of efficacy.

3.2. Difference in excipients

Excipients play a role in pharmacokinetic and pharmacodynamic of the drug, and recently we reported that they might be involved in the development of ADRs.[27] However, excipients are not considered in the law of 2006 (Legislative Decree 219/2006 in G.U. n. 142 of 21.06.2006). In this light, we can hypothesize that the difference in excipients between brand and generic allopurinol, as described in the leaflet of the two drugs and reported in Table 1could be involved in the lack of efficacy described in the present case; even if we are not able to evaluate the plasma concentration of each excipient.

Even if generic formulations are less expensive than brand name drugs, they are not always as effective and their use could not be cost-effectiveness based.

Unfortunately, in Italy there is not an orange book such as in the USA; therefore, we hope that this and other similar papers could induce AIFA, to reconsider the terms of applicability of the law n. 425/1996 previously reported (see introduction) and also to evaluate the possibility to define a book with therapeutic equivalence evaluations (considering % of active substance, % of bioequivalence and the excipients) in order to ameliorate the rationale therapeutic interchange between brand and generic formulations.

In fact, even if in our patient no other sequels due to the lack of efficacy appeared, we can't hypothesize the consequence of a switch of drug with a low therapeutic index for both patients (develops of ADRs) and clinicians (legal responsibility). Finally also the law regarding the responsibility of manufacturer may be revisited concerning the strict liability, in order to put at the same levels of responsibility generic and brand drugs as far as components are concerned.

In conclusion, we report for the first time the lack of efficacy of a generic formulation of allopurinol. At this time, since generic drugs are considered to be the same in comparison to the original drugs, they could represent only an alternative drug treatment and more data are necessary in order to well define the effectiveness of these formulations.

Ethical approval

The paper was approved from the local Ethical Committe and the patient signed the informed consent.

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Conflict of interest

We have not conflict of interest.

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